Transplant and Rejection

Introduction

When an organ is taken from someone and transplanted into someone else, how well it takes and how little rejection occurs are influenced by how closely matched the transplanted tissue is to the new immune system. The more "self" the transplanted tissue, the less reaction there will be, and the more likely the graft will be tolerated. It's all about antigens. The recipient's system will identify any antigen it doesn't recognize as "self" as foreign. Foreign antigens are attacked, presumed to be pathogens. The more antigens it sees as foreign, the more robust the immune response. The **donor** is the person from whom the organ or tissue is taken. The **host** is the **recipient** and is the person to whom the organ or tissue is given.

It's all about balancing immunity (the ability to fight infection) against tolerance (reducing rejection). Tolerance rises by having more self-antigens and fewer non-self-antigens. Alternatively, we could eliminate a host's immune system entirely to maximize tolerance, but then the patient would die of an infection. So what we actually do with organs is a little bit of both—attempt to match their "self" antigens as best we can, and give immunosuppression to a level that is tolerated, giving as little chance as possible of infection. This lesson about transplants and rejection is keyed into antigen recognition. Lesson #16: *Immunosuppression* will deal with the medications we use in transplant and autoimmune disease.

Rejection, aka Host vs. Graft Reaction (NOT Graft vs. Host Disease)

We're going to use a progressive script to make this as easy as possible to understand.

1. There are only two antigens. *"If the host has the same ONE antigen of the donated organ, it accepts the organ because it doesn't see the ONE antigen as foreign. If the organ being donated has the OTHER antigen the host doesn't have, the host will reject the organ, seeing that antigen as an invading pathogen."*

2. There are a few antigens. *"If the host has many of the same antigens as the donated organ, it is more likely to accept it, because it doesn't see those antigens as foreign. If the organ being donated has many antigens the host doesn't, the host will reject the organ, seeing those antigens as invading pathogens."*

3. Reality: thousands of antigens. "*The more shared antigens between a donated organ and the host, the more likely it will take to the new host's immune system. The more antigens the organ has that the host lacks, the more likely it is to be rejected.*"

If an organ has antigens that a host recipient does not, the host will kill the organ because it recognizes it as foreign. If an organ has antigens the host recipient already recognizes as self, the organ takes the new organ. If an organ has antigens the host recipient's immune system has already seen and developed antibodies to, it will reject it quickly and vigorously.

Notice that it was shared antigens and not paired antigens. If a donor organ is negative for an antigen, then it doesn't matter if the host is positive or negative. The best match has the fewest positive-in-donor/negative-in-host antigens. That is because we are most worried about the host immune system recognizing something new and foreign in the donor tissue, not the other way around.

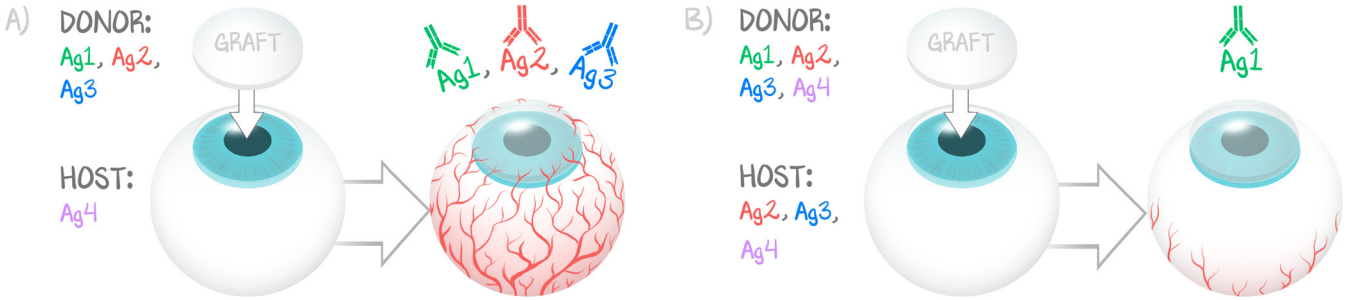


Figure 12.1: More of Non-Self = More Immune Reaction
The two images represent the magnitude of the immune response as proportional to the number of antigens felt as foreign. In (a), every antigen is seen as foreign, and so the immune system response is robust. In (b), only a single antigen is identified as foreign, and the immune response is proportional.

We're going to use a complex mouse model to explain rejection. If the italicized sentences made sense, don't bother with this. But if not, this should help clarify. Follow along with Figure 12.2.

In the model, some mice have A-antigen and some have B-antigen.

If you take an A-antigen mouse organ and transplant it into a mouse who is also A-antigen positive, the antigens match, and the organ isn't rejected.

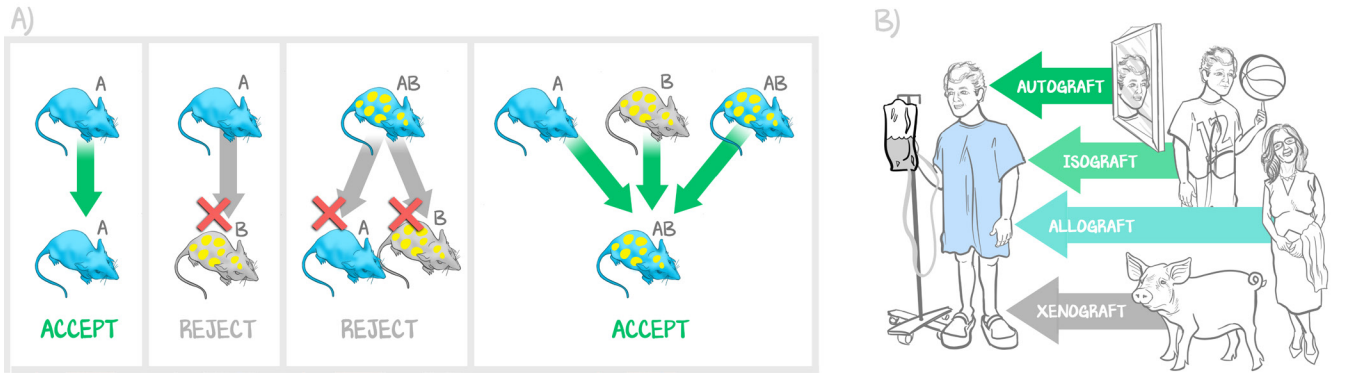


Figure 12.2: Mouse Model and Graft Types
(a) The four graft types are represented as being self, nearly identical, same species, separate species. (b) Organ rejection is about incoming antigens on the donor organ—an organism can receive a transplant that it recognizes as self and can't receive a transplant if there are antigens seen as foreign. The more antigens an organ has, to the more likely it is to be rejected.

If you take an A-antigen mouse organ and transplant it into a B-antigen mouse (one that doesn't have A-antigen), it recognizes the organ as foreign, and rejects it.

If you take a mutant mouse, who from birth has always expressed both A-antigen and B-antigen, and transplant an organ from that AB mouse into either an A mouse or a B mouse, the AB organ will be rejected. In the A-only recipient, the A-antigen is recognized as self but the B-antigen is recognized as foreign. In the B-only recipient, the B-antigen is recognized as self but the A-antigen is recognized as foreign.

If you take a mutant mouse, who from birth has always expressed both A-antigen and B-antigens, and make it the recipient, then the story inverts. An A-antigen mouse organ donor will be recognized as self. A B-antigen mouse organ donor will be recognized as self. Another AB-antigen mouse organ donor will be recognized as self.

This has a human correlate that matters in day-to-day medicine. In the previous example, see "A-antigen" as blood type, which in humans comes in four forms: A, B, AB, or O. The "+" or "–" defines Rh status. Type AB+ is the universal recipient—the person has all the antigens, so they won't recognize A, B, or Rh as foreign, and won't reject any blood type. O– is the universal donor—there are no antigens to react to—but since all other blood other than O– will have antigens registered as foreign, an O– person cannot receive any blood type other than O–.

That's a lot of writing because it explains all four permutations. The takeaway is that donor antigens must already be registered as self by the recipient. **The more antigens a donor transplant has that the recipient does not recognize as self, the worse the rejection will be.**

Types of Grafts

There are four considerations: homogeneous/autologous, syngeneic/isograft, allogeneic/allograft, and xenogeneic/xenograft.

Autologous grafts (autografts) are those that come from the same person—the donor and the recipient are the same organism. A patient's bone marrow might be sampled before giving toxic chemo, to replant the marrow that'll be destroyed by the chemo, for example (autologous stem-cell transplant). More commonly, autologous grafts are used when a flap of skin is used to recover a burn patient or a saphenous vein is harvested for a CABG. There is effectively **no risk of rejection** since all the antigens are identical to the host because they *came from the host*. The graft can still fail if the surgery goes poorly, an infection results, or the blood vessels aren't connected well. What you should learn is that "autologous grafts have no risk of rejection." Since all of the antigens are the same, there's no need for anti-rejection medications.

Isografts are genetically identical to the host, but from a different individual. One would think that identical twins would have the same genes and therefore the same self-antigens, and therefore no risk of rejection. And while isografts are the next best to autografts, isografts still express rejection. This is because there are **somatic mutations** in HLA haplotypes (the MHC of humans is HLA), such that antigen expression **even between monozygotic twins isn't as good as autografts**. Genes do most of the talking, but environment counts, too.

Allografts are from the **same species** but are otherwise **genetically dissimilar**. This is how most people get their transplanted organ—liver, heart, pancreas, kidney, lungs. Someone dies, someone else gets their liver. Who gets that liver is decided according to a balance between who needs it more ("the list") and how well **antigenically matched the recipient is**. The further from antigenic match the recipient from the donor, the higher the risk of rejection. When someone "donates a kidney to you," you don't get THEIR kidney. YOU get the best-matched kidney available, and that generous soul who donated their kidney gives their kidney directly to the system, and indirectly to the person who's the best match for it.

Xenografts are from **different species**. In line with the logic of "the worse the antigenic match, the higher the rate of rejection," it's easy to imagine that using organs of another species carries the highest risk. Xenografts are always the worst match, and are therefore used in extremely limited cases (like porcine heart valves in people not expected to outlive the graft).

The most important thing to recognize is that **the further from identical an organ gets from the recipient, the more likely, more severe, and faster the rejection will be**. Rejection will happen in all transplanted organs. Genetics determines antigens, but antigenic match is what matters the most.

Types of Rejection

Hyperacute rejection (antibody mediated) doesn't happen anymore, because we screen the serum for antibodies. This IS NOT based on "*is the antigen self or foreign?*" but rather on "*are there already preformed antibodies?*" In order to suffer hyperacute rejection, the recipient must have already been exposed to donor antigens, had an immune response, and now have preformed antibodies, memory cells, ready to strike. This happens only in large organ transplants where there's a **vascular anastomosis** and where the recipient has been **previously sensitized** (with a previous graft attempt, or antigens on the incoming organ that match previously encountered antigens). Preformed anti-donor antibodies take action right away once the vasculature is connected, leading to thrombosis and complete organ failure in minutes. The organ will turn red, white, then black. The rejection is extremely rapid, occurring within 48 hours of the transplant. This is an example of **type 2 (antibody-against-the-organ)** hypersensitivity, resulting in complement activation and clotting cascade. This doesn't happen in organ transplants, because we're cautious. However, it still occurs in the form of transfusion reactions and is clinically relevant and important to know.

Transfusion reactions historically were based on ABO incompatibility—people would transfuse A+ blood into O– patients and there would be a reaction. In today's medical real practice, ABO

incompatibility doesn't happen anymore. There are too many fail-safes in American medicine—antigen and antibody testing, protocols for proper identification of patients. However, transfusion reactions can still happen due to the presence of other antigens. In addition, because transfusion reactions illustrate rejection so well, it is a very commonly tested topic. **Blood transfusions** are considered "transplants" and ABO incompatibility is often the test question that is asked. Basically . . . match the donor blood antigens to ones that the recipient has, and rejection won't happen. But sometimes there are proteins in the blood other than ABO and Rh+/–, which can still induce a transfusion reaction. We know that ABO and Rh+ status are the two antigen types we must look for. But since there are many antigens in blood, transfusion reactions can still occur any time blood is taken from one person and given to another. This is because an antigen from the donor is recognized by the recipient's immune system as foreign, and reacts to it. The first exposure will be mild. The second exposure will be robust and severe. The bottom line is, if there are preformed antibodies, don't transfuse; if there are preformed antibodies, don't transplant. If a reaction occurs despite screening, an unrecognized antigen (or antigen not routinely screened for) may have been present.

Acute rejection is the "*normal immune response to foreign antigens*." THIS is why we do antigen testing. THIS is why we spent so much time on types of grafts and rejection. THIS is what we treat with anti-rejection meds. The fewer antigens recognized as foreign, the longer the organ lasts. The more antigens recognized as foreign, the more robust the immune response against the organ. This is considered **T-cell mediated**, but really, it's a normal immune response. APCs bring antigens to secondary lymphoid organs; T cells turn on B cells to make antibodies locally; CD8 cells turn on inflammation and activate macrophages. New antibodies bind antigens on the graft and induce the normal inflammatory response. Acute rejection takes **days** to **weeks**. **Acute rejection** occurs either when we don't start someone on immunosuppressants or when someone abruptly stops taking their rejection medications. It's limited by antigen matching and minimized by anti-rejection medications. It's a reality of transplantation of all grafts except autologous (autograft).

Chronic rejection can't be prevented. We don't know exactly how this happens. We don't have a way of stopping it. Over **years**, an organ will eventually fail. Some patients, years to a decade out, can actually come off their acute rejection medications, and last many years without them. Some people who stay faithful to their acute rejection medications still face organ failure. The reason for the discrepancy isn't totally clear.

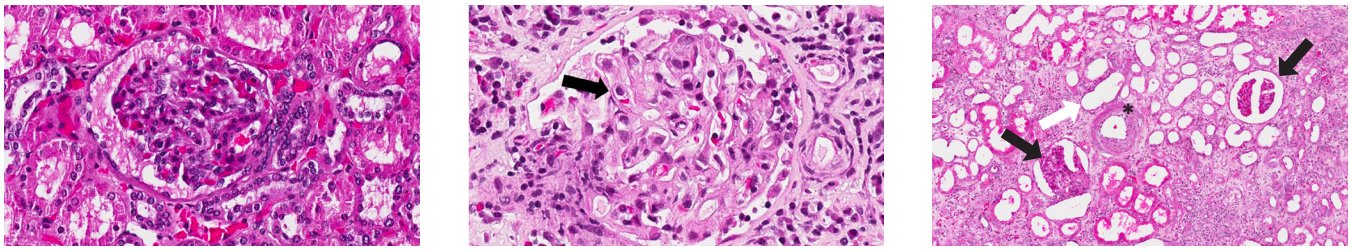


Figure 12.3: Chronic Kidney Rejection
(a) Normal kidney for comparison. (b) The glomerulus shows inflammatory cells within the capillary loops (glomerulitis), accumulation of mesangial matrix, and duplication (or multilamination) of the capillary basement membrane, referred to as "tram tracking" (black arrow). (c) Loss of tubules (black arrow), blood vessel damage with obstruction of blood flow (asterisk), glomerular sclerosis—loss of normal structures and replacement with fibrosis (white arrow).

I see organ transplantation like this:

The surgeon connects the organ. It either dies, or it lives. If it dies rapidly, think hyperacute rejection, infection, or vascular compromise. If it lives, it'll slowly fail over time because of chronic rejection. Abrupt periods of acute exacerbation of the chronic rejection can occur (acute rejection) and are due to not staying on rejection medications as they should. Nothing we do can prevent the final chronic rejection. But a patient who's faithful to her regimen can prevent acute rejection. If acute rejection flares, rapidly suppressing the immune system (pulse glucocorticoid steroids) can salvage the organ, putting it back on track for chronic rejection. Wait too long, and the organ may not recover.

If the organ dies immediately upon being connected, the vessels are thrombosed, the organ is dead, and no amount of medication will get it back. This doesn't happen anymore. Instead, it's the chronic rejection with superimposed acute rejection periods that are the course of life with a transplant.

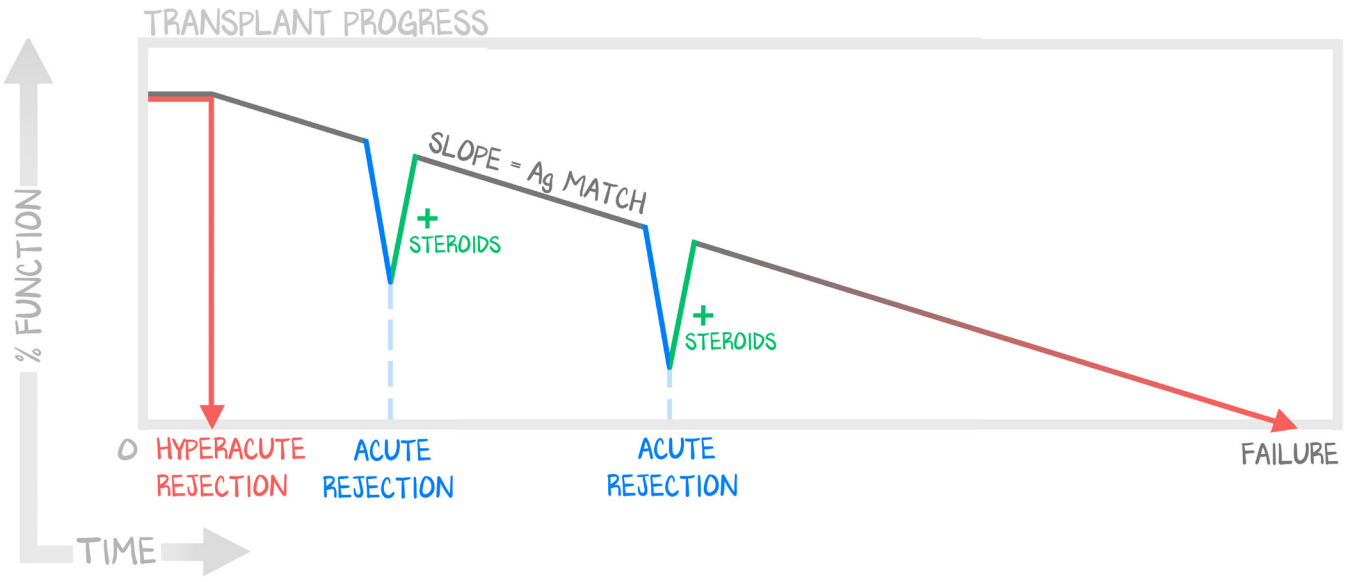


Figure 12.4: Rejection Timeline
The slow chronic rejection can never be fully prevented. Acute exacerbations of rejection are because of medication nonadherence, and transplants can be rescued if intervened on early. With hyperacute rejection, thrombosis, the vessels and the organ die; it can only be prevented, not treated.

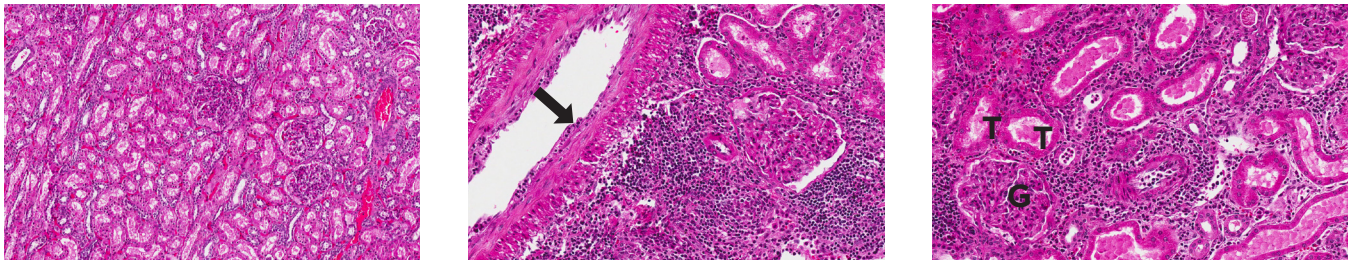
Graft vs. Host Disease

In rejection (host vs. graft reaction), if an antigen on the organ coming into the recipient is recognized as foreign by the recipient, the recipient will reject the organ. The recipient's immune system attacks the organ. Rejection. To reduce rejection, we wanted to make sure there were no antigens on the donor organ that the recipient didn't already recognize as foreign. But we didn't care if there were antigens in the recipient that weren't in the donor—an AB mouse can receive from an A mouse, an B mouse, or an AB mouse.

But graft vs. host disease occurs when **immunocompetent leukocytes from the donor** come along with the organ. This happens in transplantation of lymphoid tissue, like **bone marrow transplantation**. When a leukocyte comes over with the organ it still does what it does—recognizes foreign antigens and releases cytokines. A donor leukocyte will identify the recipient's antigens as foreign and initiate an inflammatory response. Because we don't screen for antigens in the recipient that aren't in the donor (this has no impact on rejection), it's possible that we introduce a leukocyte that recognizes the new host as foreign.

Graft vs. host disease is why the **donor** is given **immunosuppressive therapy** prior to the graft. The recipient is put on immunosuppressive therapy to prevent rejection (host vs. graft). The donor is put on immunosuppressive therapy to prevent graft vs. host. It's also why we give irradiated and leukocyte-reduced blood in bone marrow transplants—incoming leukocytes from others could hijack the recipient's immune system.

Just as there's **acute rejection** and **chronic rejection**, so too is there **acute graft vs. host disease** (often fatal) and **chronic graft vs. host disease** (skin lesions, GI lesions, and smooth-muscle deposition). It's important to recognize that graft vs. host is just a "normal" immune response by leukocytes seeing foreign antigens, just as rejection is a "normal" immune response by leukocytes seeing foreign antigens. In rejection, it's recipient leukocytes triggering inflammation and response against transplanted antigens. In graft vs. host, it's donor leukocytes triggering inflammation and response against recipient antigens. Rejection (host vs. graft) rejects the organ. Graft vs. host rejects the entire recipient.



(a) (b) (c)

Figure 12.5: Acute Kidney Rejection
(a) Normal kidney for comparison. (b) Acute rejection. Inflammatory infiltrate affecting vessels (see cells in subendothelium, arrow) and cells in glomeruli, around tubules and in the interstitium. All the purple dots between kidney structures are not supposed to be there! They are lymphocytes and represent acute inflammation. (c) High-powered view with the glomerulus (G), and the tubular structures (T), labeled. All other purple dots are inflammatory cells.

Citations

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